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Ki67 immunoexpression in ovarian tumours

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Abstract
Background: Mitotic count is a traditional and practical important method to determine proliferative activity. Immunohistochemical detection of proliferative cells is a alternative way to determine the proliferative potential of tumour, and the expression of Ki67antigen has a widely used marker.Ki67 is a nuclear protein expressed in cells during the active phase of the cellular cycle(G1, S, G2& M) and absent in G0 phase. The determination of growth fraction using Ki67 is a simple method and has been shown to have a prognostic value in a variety of malignancies. ***Material and methods : -*** *The present study "Ki67 immunoexpression in ovarian tumours " was carried out in the Department of Obstetrics and Gynaecology in collaboration with the department of Pathology , RIMS, Ranchi, in the period between May 2013 to October 2014. Sample size were 100.*
Results: *mean Ki67 index of benign ovarian tumours is 3.7±2.64%, malignant ovarian tumours is 40.15±9.3%, borderline ovarian tumours is 17±2.83%. statistical difference observed between benign, borderline, malignant ovarian tumours while no statistical difference found between different histological types of ovarian tumours.*
Conclusion: *In the present study,high Ki67 index observed in malignant ovarian tumours hence suggest the aggressive behaviour of the tumour and poor clinical outcomes.*
Keywords: *ovarian tumour, Ki67, immunohistochemistry.*

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I. Introduction

Ovarian cancer is the second most common of all genital cancers and accounts for 10-15% of all gynaecological cancers in developing countries.[1] Incidence of ovarian cancer in India is 4.6/100000. It is the fourth most common cause of deaths in women exceeded only by breast , colon and lung malignancies.[2] A woman risk of birth having cancer sometime in her life is 1 to 1.5 % and that of dying of ovarian cancer is almost 0.5%.[3] 70% of the women diagnosed with ovarian carcinoma have advanced disease at the time of diagnosis.[4]

Important prognostic factors include stage of disease, age at diagnosis, histological type and grade, ploidity, and the amount of residual disease after primary surgery [5, 6]. Furthermore, high proliferative activity in the ovarian tumor has been shown to imply a poor prognosis [7, 8].

Until now, the heterogeneous group of ovarian carcinomas has been treated with the same chemotherapy regimens [9]. In the future, subclassification of ovarian carcinomas will be important in order to provide a more tailored therapy for this malignancy. Thus, the cellular proliferation status of a tumor may be a diagnostic, as well as a prognostic tool [8].

Mitotic count is a traditional and practical method to determine proliferative activity, but is hampered by several disturbing factors [10]. Immunohistochemical detection of proliferating cells is an alternative way to determine the proliferative potential of a tumor, and the expression of Ki-67 antigen has become a widely used marker. This antigen is expressed during all active phases of the cell cycle (G1, S, G2, and mitosis), and the monoclonal Ki-67 antibody (MIB-1) reacts with the nuclear Ki-67 antigen expressed in cycling cells [11]. High expression of Ki-67/MIB-1 has been found to indicate a poor prognosis in several cancers, including ovarian cancer [7, 12-17]. Uncontrolled cellular proliferation is one of the most important biological mechanisms involved in oncogenesis.[18]The high proliferation rate has been associated with tumour aggressiveness and correlates with the prognosis and other known clinicopathological features of the tumour. The fraction of Ki67 positive cells is often correlated with clinical course of cancers.[17]Ki67 expression in different ovarian tumours has been studied by various authors across the world. However there is paucity of such a study in Indian literature.[19]

II. Objective

To evaluate the biological significance of Ki67 expression by immunohistochemistry in ovarian tumours.

III. Material And Methods

Total of 100 patients who underwent laparatomy at Dept. Of Obstetrics and Gynaecology Rajendra Institute of Medical Sciences, Ranchi in the study period of May 2013 to October 2014 were recruited for the study. Ki67 expression by immunohistochemistry in surgical specimen of ovarian tumours was done at Department of Pathology , Rajendra Institute of Medical Sciences , Ranchi.

PROCEDURE OF IMMUNOHISTOCHEMISTRY
Tissue processing and section cutting:
Fixation: done with 10% formalin
Dehydration: done in ascending grade of isopropyl alcohol.
Clearing: done with xylene
Impregnation : carried out with the help of wax
Embedding and blocking: embedding was done with help of wax and blocking was done in L blocks(Leukhart's block)
Section cutting : 4-5 mm thick section were taken with the help of rotatory microtome.
Immunohistochemistry was done by indirect immunoperoxidase technique(novocastra reagents by leica Microsystems).
Respective section from all the 100 cases were studied by selecting the areas showing good cellularity . A minimum of 200 cells per section were counted for Ki67 positivity and expressed as a percentage. Cell showing distinctive brown staining of nuclei and nucleoli were counted as positive.
Immunohistochemical expression of Ki67 in its significance was evaluated in ovarian tumours.

IV. Results

The present work " Ki-67 immunoexpession in ovarian tumours" was carried out in 100 surgical ovarian specimens of patients who underwent oopherectomy or total abdominal hysterectomy with unilateral/bilateral salpingo-oopherectomy as per indications.

TABLE 1:

Types of ovarian tumours	Mean Ki-67 index (%)
Benign ovarian tumours (N=61)	3.7 ±2.64%
Malignant ovarian tumours (N=32)	40.15 ±9.63%
Borderline ovarian tumours(N=7)	17 ± 2.83%

TABLE 2:

	Histological subtypes of ovarian tumours	Mean Ki-67 index(%)
1	Serous cystadenoma	5.88± 2.62%
2	Mucinous cystadenoma	3.72±1.75%
3	Serous cystadenocarcinoma	41.64±10.15%
+4	Mucinous cystadenocarcinoma	40.3±8.11%
5	Benign germ cell tumours	2.8±1.32%
6	Malignant germ cell tumours	35.29±6.99%
7	Sex cord stromal tumours	4±2.44%
8	Metastatic adenocarcinoma	44±2.83%
9	Borderline serous cystadenoma	18.8±4.11%
10	Borderline mucinous cystadenoma	17±2.64%

Applying student t test to the above observations, and p value of <0.05 is considered statistically significant. Thus a statistically significant difference in Ki-67 positivity seen between benign , malignant and borderline ovarian tumours . However no significant difference was observed between different histological types of ovarian tumours.

V. Discussion

Ki-67 protein is a cellular marker for proliferation.It is strictly associated cell proliferation .ki-67 is an excellent marker to determined the growth fraction of a cell population.
In the present study ;

- Mean of ki-67 positivityin benign serous tumours is 5.58±2.26% similar to the finding reported by Garzetti et al 1995(7.5- 12%),Kobel et al 2008,2.5%[20],Choudhary et al 2011(3.2±3.7)[19] ,Guro Aune et al 2011[21],Luminata et al 2012.(1.8)[22]`

- Mean ki-67 positivity of benign mucinous tumours(n =18) is 3.72%±1.75% with immunostained cells ranging from 0 to 5 .Similar observations seen by Terlikowski S et al(1999)[23]& Kamal et al(2011).[24]
- Mean ki67 positivity in serous cystadenocarcinoma and mucinous cystadenocarcinoma were 41.64±10.15% and 40.3±8.11% respectively.
- Mean ki67 index for borderline ovarian tumours was 17±2.83%.Similar findings reprted by Guro Aune et al(2011),Luminata et al (2012).
- Benign germ cell tumours presented with mean ki67 index of 2.8±1.32% while the malignant germ cell tumours presents 32.29±6.99%.
- Sex cord stromal tumours showed mean ki67 index of 4±2.83%.

In the present study,significant different of ki67 positivity was observed between malignant , borderline and benign ovarian tumours while no statistical significant difference was seen between various histological type of ovarian tumours.Choudhury et al(2011) and Guro Aune et al (2011) studies showed similar observation.

Ki67 immunoexpression was more obvious in malignant tumours compared to benign and borderline tumours. This highlights the role of nuclear factor in tumour growth. The low Ki67 immunoreaction in borderline tumours suggests that increase expression occurs later in the development of carcinoma.

VI. Conclusion

Ki67 expression can be useful in evaluating aggressive tumour behaviour and also for differentiating between carcinomas and borderline tumours and for planning the future management by allowing the individualization of the treatment..

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